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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,734	10/08/2003	David M. Goldenberg	329241	5299

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/680,734	GOLDENBERG ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2008*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,10,11,44,49-51 and 108-114* is/are pending in the application.
  4a) Of the above claim(s) *44 and 49-51* is/are withdrawn from consideration.
5)☒ Claim(s) *113* is/are allowed.
6)☒ Claim(s) *1,6,7,10,11,108-112 and 114* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  a)☐ All b)☐ Some * c)☐ None of:
    1.☐ Certified copies of the priority documents have been received.
    2.☐ Certified copies of the priority documents have been received in Application No. _____.
    3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
  * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
  Paper No(s)/Mail Date *9/9/08*.
4) ☐ Interview Summary (PTO-413)
  Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/10/08 has been entered.

2. Claims 1, 6, 7, 10, 11, 44, 49-51 and 108-114 are all the pending claims for this application.

3. Claims 44 and 49-51 are withdrawn from examination.

4. Claims 110-114 were added in the Response of 9/10/08.

5. Claims 1, 6, 7, 10, 11 and 108-114 are all the claims under examination.

Information Disclosure Statement

6. The IDS filed on 9/9/08 has been considered and entered with the exception of those references cited in a previous 1449 or 892 form. To avoid redundancy, those references have been stricken on the form. The copy of the initialed 1449 form is attached.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement (1)

7. The rejection of Claims 1, 6, 7, 10, 11, 108, 109 and new Claims 110-112 and 114 under 35 U.S.C. 112, first paragraph, is maintained in lacking enablement for any combination therapy (any anti-CEA-antibody with any apoptotic agent) producing a synergistic effect in treating human medullary thyroid carcinoma or human colorectal cancer.

The rejection was set forth in the Office Action of 10/22/07 as follows:

> "...Claim 1 encompasses any anti-CEA Mab (other then MN-14 of Claims 6 and 7), any apoptosis agent (other than those in Claims 10, 11 and 108) and any combination, which are not enabled by the specification as set forth in the Office Action of 6/6/07.
>
> For example, Example 9 of the specification describes using antibodies targeting different epitopes than huMN-14 (i.e., NP1, NP3, MN3, MN15; (Sharkey, R. M., et al., Cancer Res, 50:2823-2831,1990). But it is not readily apparent from the discussion whether and how these antibodies performed differently than the MN-14 antibody under the same test conditions. Thus, absent a further showing, Applicants have only disclosed the MN-14 antibody having the instant claimed properties. Applicants' specification does not disclose any other antibody than huMN-14 having a synergistic effect in combination with selected apoptosis agents for treating "human medullary thyroid carcinoma or human colorectal cancer". Thus Applicants have not demonstrated a reasonable number of embodiments under the *Wands* decision (8 USPQ2d 1400 (Fed. Cir. 1988)) for the anti-CEA Mabs meeting the limitation of step (i). Applicants have not demonstrated a reasonable number of embodiments of compositions comprising the anti-CEA Mab of step (i) in combination with any apoptosis agent having a synergistic effect on "human medullary thyroid carcinoma or human colorectal cancer". Absent an enabling disclosure for the scope of the claims, one of ordinary skill in the art at the time of filing would not have been enabled to have practiced the scope of the invention for Claim 1 without undue experimentation."

For further review, the rejection was maintained in the Office Action of 4/22/08 and the Advisory Action of 9/10/08 as follows:

"Applicants' allegations on pp. 5-6 of the Response of 1/17/08 have been considered and are not found persuasive. Applicants allege that the claims now encompass a narrower class of anti-CEA antibodies in view of amended claim 1; the specification in view of the art discloses how to determine whether an anti-CEA antibody possesses all of these properties; anti-CEA antibodies non-reactive with human granulocytes are known in the art (cited in USPN 5,843,708; Can. Res. 50(7):2128-2134 (1990); Can. Res. 52(8):2329-2339); the specification describes several antibodies non-reactive with granulocytes, various therapeutic agents, Example 6 shows how to determine therapeutic specificity and Examples 7-18 illustrate therapeutic effect of the claimed composition. Applicants allege undue experimentation is not required to make and use the inventive composition.

Examiner's Reply

The examiner respectfully submits that the subclass of anti-CEA monoclonal antibodies encompassed by the claims has not in any way been proved by Applicants much less by the cited art to possess all of the instant required properties, namely,

a) the antibody is unreactive with human granulocytes

b) the antibody has an IgG human constant region

c) the antibody sensitizes any CEA-expressing cancer (in vitro or in vivo) to any subsequently administered therapeutic agent, where the therapeutic agent is an apoptosis agent, *and*

d) the combined effect of the antibody and apoptosis agent is more effective than either moiety alone or the sum effect of either moiety given individually in treating human medullary thyroid carcinoma or human colorectal cancer.

From the list of anti-CEA antibodies known to be unreactive to human granulocytes (i.e., CE25, T84.66, II-10, II-7, BU-101 and 26/3/13; p. 6 of the Response) none are disclosed in any of the three references as having an inherent or implicit property of both c) and d) above. Applicants make an assumption without evidentiary support that any one of these antibodies would necessarily have the same properties as the MN-14 antibody. Further, and pursuant to MPEP 2144.03, "ordinarily there must be some form of evidence in the record to support an assertion of common knowledge."

From the list of apoptotic agents referred to in the specification on p. 6 of the Response, none are shown to produce the effect of d) above when combined with any one of the list of anti-CEA antibodies in treating human medullary thyroid carcinoma or human colorectal cancer. Applicants make the assumption without evidentiary support that any one of the apoptotic agents could be combined with any one of the anti-CEA antibodies to produce a composition necessarily having the same properties as the composition comprising the MN-14 antibody and an apoptotic agent.

Additionally the examiner submits that Applicants have not proven by a preponderance of the evidence that combining any one of the antibodies, CE25, T84.66, II-10, II-7, BU-101 and 26/3/13, with any apoptotic agent would reliably and *predictably* yield a composition having the same properties (i.e., c) and d) above) as one comprising the MN-14 antibody (MPEP 706). Further Applicants' summary of the test for enablement on p. 6, ¶4 of the Response excludes any mention of predictability. MPEP 2164.04 states in part:

"The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability" (citing *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)).

"In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work."

The examiner respectfully submits that all Applicants have provided in this phase of the prosecution proceeding is lists of antibodies and lists of apoptotic agents. Applicants allege that any combination from any list would have all of the same properties as the limited working examples for anti-CEA antibodies, the MN-14 antibody, that they define in their specification. The cited references define lists of reagents related in scope to the instant composition of Claim 1, but do not address the problem to be solved by the instant invention (MPEP 2164.05(a)), namely a composition comprising an anti-CEA antibody and an apoptotic agent that when combined are more effective (i.e., synergize) at treating human medullary thyroid carcinoma or human colorectal cancer than either reagent alone and where the anti-CEA antibody chemosensitizes any cancer for the therapeutic agent."

Applicants' allegations on pp. 8-11 of the Response of 9/10/08 have been considered and are not found persuasive. Applicants allege Example 2 discloses combination therapy with human medullary thyroid tumor cells and shows a synergistic effect. Examples 7 and 8 show combined therapy with a human MTC (medullary thyroid cancer) xenograft model system and synergistic effects; Example 9 describes use with colon cancer cells and concludes, "The results show that co-administration of hMN- 14 and CPT- 11 to nude mice bearing GW-39 lung micrometastases increases survival beyond the effect of either modality alone." Example 14 discloses that for an advanced colon cancer model, "No effect of hMN-14 by itself is apparent under these conditions, and only a modest effect of CPT-11 (p0.05) was observed...Combination therapy with hMN-14 CEA MAb and CPT-11 significantly prolongs survival of an animal with advanced human colonic tumor metastasis." Examples 15-17 confirm the synergistic effects ofhMN-14 and CPT- 11; "Thus, at least two of the apoptotic agents, DTIC and CPT-11, are demonstrated to exhibit the effect of d) when used in combination with the anti-CEA hMN- 14 antibody."

Response to Arguments

The examiner acknowledges the extent of experimentation pointed out by Applicants and that two of the apoptotic agents, DTIC and CPT-11, are demonstrated to exhibit a synergistic effect when used in combination with the anti-CEA hMN- 14 antibody. However, the rejected claims are not limited to the enabling synergistic combination therapies disclosed in the specification. It is noted that the features upon which applicant relies (i.e., the apoptotic agents, DTIC and CPT-11, are demonstrated to exhibit a synergistic effect when used in combination with the anti-CEA hMN- 14 antibody) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

It is the examiner's position that the art recognizes the unpredictability of drug combinations being synergistic. In determining a synergistic reaction, the ordinary artisan would take a single drug and distribute it into two containers, A and B, or combine different mixtures of A and B, e.g., 10A + 0B, 9A + 1B, 5A + 5B, 1A + 9B, 0A + 10B.

> $A/A_e + B/B_e = Z$ where $Z = 1$ is additive, $Z<1$ is synergy and $Z>1$ is antagonism, where A_e and B_e are equieffective doses of drug.

Dose response curves are rarely, if ever, linear except with ionizing radiation. Most dose response curves are hyperbolic and result from drug-receptor interactions, a binding phenonmenon. Thus the solution to this problem is drugs should be compared at equieffective doses, A_e and B_e, by titrating the drug to endpoint. Any equivalent effectiveness may be used; but, 50%, the midpoint is most common. (see Berenbaum Clin. Exp. Immunol. 28:1-18 (1977); Berenbaum Pharmacol. Rev. 41:93-141 (1989)); and Tallarida "Drug Synergism and Dose Effect Analysis" Ed. Chapman & Hall (2000), pp. 1-71.

In fact, Applicants have not provided sufficient evidence showing that a reasonable number of anti-CEA antibodies (other than the hMN-14 antibody) and could be combined with any apoptosis agent (other than DTIC and CPT-11) to produce a synergistic effect in treating human medullary thyroid carcinoma or human colorectal cancer. Thus the showing of synergism is not commensurate in scope with the claims.

The rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement (2)

8. The rejection of Claims 1, 6, 7, 10, 11, 108, 109 and new Claims 110-112 and 114 under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for using any anti-CEA antibody to *sensitize* any cancer in vivo to a therapeutic agent much less where the subject is a human.

For purposes of review, the grounds for rejection were set forth in the Office Action of 4/22/08 and maintained in the Advisory Action of 9/10/08 as follows:

"Nature of the Invention/ Skill in the Art

The interpretation of the claims is of record and as discussed above. The claims are examined for an intended use for administering the composition or molecules of the composition (see indefiniteness rejection discussed above) in sensitizing a cancer in vivo in any subject with any anti-CEA Mab.

The relative skill in the art required to practice using the composition in vivo or the components of the composition in vivo is a clinical oncologist or veterinarian.

Disclosure in the Specification

The specification supports administration of the naked anti-CEA Mab to a cancer expressing CEA sensitizes the cancer to the subsequent administration of a cancer therapeutic agent at [107; 0293 and 0294] of the published specification, or which otherwise corresponds to Example 16. Example 16 shows that pre-treatment of the GW-39 intrapulmonary cancer in a GW-39 intrapulmonary micrometastasis mouse model with naked hMN-14 CEA Mab prior to CPT-11 treatment prolonged the survival of mice by additional 58% above CPT-11 alone.

The specification contemplates using the compositions to treat animal and human subjects. The specification does not disclose chemosensitizing a human medullary thyroid carcinoma using any anti-CEA antibody much less the MN-14 Mab. Thus, the specification is not enabling for the broad class of anti-CEA antibodies that could sensitize any cancer in vitro much less in vivo where the subject was a human.

Prior Art Status: MN-14 sensitization of cancers

Stein (Cancer 94:51-61 (1/1/2002); cited in the PTO 892 form of 10/22/07) teaches compositions for treating nude mice bearing human medullary thyroid tumor comprising the radiolabeled anti-CEA Mab MN-14 in combination with the apoptosis agents, doxorubicin, DTIC, cyclophosphamide, and vincristine, to produce a synergistic effect "significantly enhanced over that observed with either single modality therapy" (p. 59, Col. 2, ¶1).

Blumenthal (54:142-151 (1994) Abstract; cited in the PTO 892 form of 10/22/07) compares the effect of conventional 5-FU and radiolabeled MN-14 Mab on human xenograft tumor cell lines (LoVo, HT-29, DLD-1, HCT-15, LS174T, Moser, Gw-39 and WidR) in mice. Blumenthal suggests that MN-14 therapy may have advantages over conventional 5-FU therapy alone.

Each of these references teaches radio-sensitization using a radiolabeled MN-14 Mab.

Prior Art Status: in vitro/in vivo translation of antibody therapy

In general, the field of art recognizes recombinant antibodies such as humanized, scFv and multimeric scFvs (diabodies) as the next generation of Ab-based molecules in treatment of solid tumors. But the complexity and difficulty of antibody delivery for cancer treatment is underscored by Beckman et al. (Cancer 109:170-179 (2007); cited in the PTO 892 form of 6/6/07) who discuss the relevance of achieving a) tumor penetration and retention and b) favorable plasma pharmacokinetics in promoting tumor exposure. “Studies in tumor-bearing rodents are often confounded by lack of normal tissue reactivity with Ab constructs directed toward human Ags, but studies in transgenic animals can be performed in some instances to alleviate this issue. For example, CEA-transgenic mice were used to test anti-CEA mAbs and revealed specific accumulation in normal gastrointestinal mucosa as well as in adenomas and tumors…Theoretical models may help to understand and interpret experimental results, to prioritize further experimental work, and to translate experiments in murine systems to humans” (p. 175, Col. 2, ¶5 to p. 176, Col. 1, ¶1). Finally, “In optimizing Ag-Ab constructs for affinity and other properties it is well to bear in mind the mechanism of cell kill, and the requirements in terms of percent occupancy and long residence time are required for cell kill, high affinity may be preferable and the approach would have to be to treat the outer layer of the tumor with each course. Tumors are genetically unstable, however, and if antibody therapies take too long to penetrate them, may acquire resistance” (p. 176, Col. 1, ¶2).

Further, the translation of any in vitro studies to in vivo applications much less into human trials is understood as being unpredictable at the time of the invention and remains so. Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)) conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that “the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents” and “New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target” (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006); cited in the PTO 892 form of 6/6/07) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because “many more [drugs] that show positive results in mice have little or no effect in humans” (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar. One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not necessarily correlate with results expected in human CEA-expressing tumors.

Thus based on the insufficient guidance in the specification and the general state of the art recognizing the unpredictability for treating any cancer in vivo with an antibody, much less extrapolating any animal model data to human, one skilled in the art would be required to perform undue trial and error experimentation in order to make and/or practice the full scope of the instant claimed composition.”

Applicants’ allegations on pp. 8-11 of the Response of 9/10/08 have been considered and are not found persuasive. Applicants did not distinguish this enablement rejection from the previous. Thus in the interest of advancing prosecution, the summary of their arguments are incorporated herewith.

Response to Arguments

Applicants have not demonstrated the antibody-mediated sensitizing effect of any CEA antibody for any therapeutic agent in a human medullary thyroid carcinoma model or human colorectal cancer model in vivo. Applicants have not provided sufficient evidence showing that a reasonable number of anti-CEA antibodies (other than the hMN-14 antibody) and could sensitize human medullary thyroid carcinoma or human colorectal cancer in vivo to any apoptosis agent (other than DTIC and CPT-11). Thus the showing of sensitization is not commensurate in scope with the claims.

Conclusion

9. Claim 13 is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Partial Signatory Authority